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L3: Entry 74 of 228 File: USPT Jun 25, 2002

US-PAT-NO: 6410255
DOCUMENT-IDENTIFIER: US 6410255 B1

TITLE: Optical probes and assays

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Hamman; Brian D.	Poway	CA		
Rodems; Steven M.	Poway	CA		
Makings; Lewis R.	Encinitas	CA		

US-CL-CURRENT: 435/23; 435/21

CLAIMS:

We claim:

1. A method for measuring a post-translational modification activity, comprising:

a) contacting a sample with an engineered optical probe, said engineered optical probe comprising:

a polypeptide comprising a first probe moiety,

wherein said polypeptide comprises a recognition motif for a post-translational type modification within said polypeptide, and a protease site located within said polypeptide; and

wherein post-translational type modification of said recognition motif modulates the rate of cleavage of said polypeptide by a protease with specificity for said protease site,

b) contacting said sample and said engineered optical probe with a protease with specificity for said protease site, and

c) detecting a change in at least one optical property of said engineered optical probe.

2. The method of claim 1, wherein said polypeptide does not exceed 15 amino acids in length.

3. The method of claim 1, wherein said polypeptide does not exceed 50 amino acids in length.

4. The method of claim 1, wherein said optical property comprises a fluorescent property.

5. The method of claim 4 wherein said fluorescence property is fluorescence anisotropy.

6. The method of claim 5, wherein said polypeptide is attached to a solid matrix.

7. The method of claim 1, further comprising a fluorescent quencher attached to said polypeptide, wherein said recognition motif and said protease site are located between said first probe moiety and said fluorescent quencher.

8. The method of claim 1, wherein said optical property is fluorescence emission.

9. The method of claim 8, wherein said polypeptide is attached to a bead.

10. The method of claim 1, further comprising a second probe moiety attached to said polypeptide, wherein said recognition motif and said protease site are located between said first probe moiety and said second probe moiety.

11. The method of claim 10, wherein said optical property is fluorescence resonance energy transfer.

12. The method of claim 8, wherein said optical property is bioluminescence/emission.

13. The method of claim 8, wherein said protease is one of the following caspase 3, cathepsin G, chymotrypsin, elastase, endoproteinase Asp-N or endoproteinase Glu-N.

14. The method of claim 8, wherein said post-translational type activity is protein tyrosine kinase activity or protein tyrosine phosphatase activity.

15. The method of claim 8, wherein said post-translational type activity is protein serine or threonine kinase activity or protein serine or threonine phosphatase activity.

16. The method of claim 1, wherein said first probe moiety comprises a fluorophore selected from the group consisting of fluorescein-5-isothiocyanate, dichlorotriazinylaminofluorescein, tetramethylrhodamine-5 or 6-isothiocyanate, 1,3-bis-(2-dialkylamino-5-thienyl)-substituted squarines, carboxyfluoroscein; 5 or 6-carboxytetramethylrhodamine; and 7-amino-4-methylcoumarin-3-acetic acid.

17. The method of claim 1, wherein said first probe moiety comprises coumarin.

18. The method of claim 17, wherein said first probe moiety comprises 7-hydroxy coumarin.

19. The method of claim 1, wherein said first probe moiety comprises rhodamine.

20. The method of claim 19, wherein said first probe moiety comprises rhodamine B.

21. The method of claim 1, wherein said first probe moiety comprises fluorescein.

22. The method of claim 21, wherein said first probe moiety comprises fluorescein-5-isothiocyanate.

23. The method of claim 11, wherein said first probe moiety comprises a lanthanide complex.

24. The method of claim 11, wherein said first probe moiety, or said second probe moiety comprises a fluorophore selected from the group consisting of fluorescein-5-isothiocyanate, dichlorotriazinylaminofluorescein, tetramethylrhodamine-5 or 6-isothiocyanate, 1,3-bis-(2-dialkylamino-5-thienyl)-substituted squarines, carboxyfluoroscein; 5 or 6-carboxytetramethylrhodamine; and 7-amino-4-methylcoumarin-3-acetic acid.

25. The method of claim 11, wherein said first probe moiety, or said second probe moiety comprises coumarin.

26. The method of claim 11, wherein said first probe moiety, or said second probe moiety comprises 7-hydroxy coumarin.

27. The method of claim 11, wherein said first probe moiety, or said second probe moiety comprises rhodamine.

28. The method of claim 27, wherein said first probe moiety, or said second probe moiety comprises rhodamine B.

29. The method of claim 11, wherein said first probe moiety, or said second probe moiety comprises fluorescein.

30. The method of claim 29, wherein said first probe moiety, or said second probe moiety comprises fluorescein-5-isothiocyanate.

31. The method of claim 11, wherein said first probe moiety, or said second probe moiety comprises a lanthanide complex.

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Makings; Lewis R.	Encinitas	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 09/ 306542 [PALM]
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INT-CL: [07] C12 Q 1/37, C12 Q 1/42

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US-CL-CURRENT: 435/23; 435/21

FIELD-OF-SEARCH: 435/23, 435/21

PRIOR-ART-DISCLOSED:

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6/24

Ras farnesylation as a target for novel antitumor agents: Potent and selective farnesyl diphosphate analog inhibitors of farnesyltransferase (p 121-137)
Veeraswamy Manne, Carolyn S. Ricca, Johnni Gullo Brown, Anne V. Tuomari, Ning Yan, Dinesh Patel, Robert Schmidt, Mark J. Lynch, Carl P. Ciosek Jr., Joan M. Carboni, Simon Robinson, Eric M. Gordon, Mariano Barbacid, Bernd R. Seizinger, Scott A. Biller
Drug Developmnet Research vol. 34, 1995

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Search Results - Record(s) 1 through 19 of 19 returned.

☐ 1. 20030203407. 05 Mar 03. 30 Oct 03. Compositions and methods for monitoring the phosphorylation of natural binding partners. Craig, Roger K., et al. 435/7.1; 530/388.26 G01N033/53 C07K016/40.

☐ 2. 20030082827. 24 Feb 00. 01 May 03. Methods And Compositions Using Protein Binding Partners. Craig, Roger K, et al. 436/518; G01N033/543.

☐ 3. 20030079235. 16 May 02. 24 Apr 03. Assay for measuring enzyme activity in vivo. Craig, Roger Kingdon, et al. 800/3; 424/9.6 435/6 A61K049/00 G01N033/00 C12Q001/68.

☐ 4. 20020090643. 26 Feb 99. 11 Jul 02. COMPOSITIONS AND METHODS FOR MONITORING THE PHOSPHORYLATION OF NATURAL BINDING PARTNERS. CRAIG, ROGER K., et al. 435/7.1; G01N033/53.

☐ 5. 6852906. 16 May 02; 08 Feb 05. Assay for measuring enzyme activity in vivo. Craig; Roger Kingdon, et al. 800/3; 800/22 800/278 800/288 800/8. G01N03100 A01K06700 A01K067033 A01H00100 C12N01582.

☐ 6. 6670144. 23 Feb 00; 30 Dec 03. Compositions and methods for monitoring the phosphorylation of natural binding partners. Craig; Roger K., et al. 435/21; 435/183 435/188 435/188.5 435/194 435/7.8 435/7.9 435/7.91. G01N033/53 G01N033/542 C12Q001/42 C12N009/00 C12N009/96.

☐ 7. 6656696. 26 Feb 99; 02 Dec 03. Compositions and methods for monitoring the phosphorylation of natural binding partners. Craig; Roger K., et al. 435/7.6; 424/9.6 435/188 435/21 435/7.1 435/7.4 435/7.7 435/7.71 435/7.72 435/7.9 436/537 436/544 436/546 536/25.32. G01N033/53 G01N033/573 G01N033/543 C12Q001/42 C12Q009/96.

☐ 8. 6465199. 26 Feb 99; 15 Oct 02. Compositions and methods for monitoring the modification of natural binding partners. Craig; Roger K., et al. 435/7.4; 435/7.1. G01N033/573 G01N033/53.

☐ 9. US 6670144B. Screening candidate modulator of enzymatic activity of kinase or phosphatase, by detecting binding or disassociation of isolated natural binding domain to/from binding partner. COLYER, J, et al. C12N009/00 C12N009/96 C12Q001/42 G01N033/53 G01N033/542.

☐ 10. US20030203407A. Natural binding domain useful in monitoring the activity of enzymes comprises site for post-translational phosphorylation and binds to its partner depending on phosphorylation or dephosphorylation of the site. COLYER, J, et al. C07K016/40 G01N033/53.

☐ 11. US 6465199B. Monitoring enzyme activity, by detecting binding or dissociation of isolated natural binding domain and its binding partner as a result of contacting the natural binding domain and binding partner with the enzyme. COLYER, J, et al. G01N033/53 G01N033/573.

☐ 12. US20020090643A. Monitoring enzyme activity by detecting binding of isolated natural binding domain and its binding partner or dissociation of the domain from the partner as result of contacting the domain or partner with the enzyme. COYLER, J, et al. C12N009/96 C12Q001/42 G01N033/53 G01N033/543 G01N033/573.

☐ 13. WO 200136617A. Measuring cellular enzyme activity in transgenic non-human organism comprising nucleic acid constructs encoding binding domain and its partner, by measuring changes in physical characteristics in cells of organism. COLYER, J, et al. A01H001/00 A01K067/00 A01K067/027 A01K067/033 A61K049/00 C12N009/00 C12N015/00 C12N015/62 C12N015/82 C12Q001/68 G01N031/00 G01N033/00.

☐ 14. WO 200050896A. Monitoring the enzymatic activity as a function of the interaction of binding partners, by use of a protein modifying enzyme. COLYER, J, et al. C12Q001/42 C12Q001/48 G01N033/542.

☐ 15. WO 200050902A. High throughput assay for monitoring modification of polypeptides and modulation of the modifications. COLYER, J, et al. G01N033/68.

☐ 16. WO 200050630A. Measuring different enzyme activities simultaneously by contacting with a binding domain and a binding partner having a site post-translationally modifiable by the enzyme and measuring interaction between them. COLYER, J, et al. C12Q001/00.

☐ 17. WO 200050901A. Determining the conformational state of a protein, comprises contacting the protein with a labeled binding protein and assessing the labeling of the protein. COLYER, J, et al. C12Q001/00 G01N033/543 G01N033/563 G01N033/58 G01N033/68.

☐ 18. WO 200050635A. Labeled polypeptide binding partner compositions useful for monitoring protease activity by detecting signal modulation. COYLER, J, et al. C07K014/00 C12Q001/00 C12Q001/37 G01N033/35 G01N033/53.

☐ 19. WO 200050631A. Compositions and methods for monitoring the modification of natural binding partners, useful for monitoring post-translational modifications of proteins and enzymes. COLYER, J, et al. C07K002/00 C07K014/00 C12N015/09 C12Q001/00 C12Q001/25 C12Q001/34 C12Q001/42 C12Q001/48.

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Oncogene. 1995 May 4;10(9):1763-79. Related Articles, Links

Bisubstrate inhibitors of farnesyltransferase: a novel class of specific inhibitors of ras transformed cells.

Manne V, Yan N, Carboni JM, Tuomari AV, Ricca CS, Brown JG, Andahazy ML, Schmidt RJ, Patel D, Zahler R, et al.

Division of Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.

We describe the biological properties of a new class of potent farnesyltransferase (FT) inhibitors designed as bisubstrate analog inhibitors. These inhibitors incorporate the structural motifs of both farnesyl pyrophosphate and the CAAX tetrapeptide, the two substrates of the reaction catalyzed by FT. Both the phosphinate inhibitor, BMS-185878, and the phosphonate inhibitor, BMS-184467, exhibited higher in vitro FT selectivity than some of the previously reported CVFM peptidomimentics and benzodiazepine analogs. Xenopus oocyte maturation induced by microinjected oncogenic Ras proteins was blocked by coinjected BMS-184467 and BMS-185878. However, both inhibitors showed poor cell activity presumably because of the doubly charged nature of the compounds. Thus, masking the charge on the carboxylate ion markedly improved the cell permeability of BMS-185878, leading to BMS-186511, the methyl carboxyl ester prodrug. BMS-186511 inhibited FT activity in whole cells as determined by inhibition of p21 Ras protein processing, inhibition of farnesylation of proteins including Ras and the accumulation of unfarnesylated Ras proteins in the cytosolic fraction. While the cellular effects of these bisubstrate analog inhibitors had no significant effect on growth of untransformed NIH3T3 cells, they produced pronounced inhibition of Ras transformed cell growth. Both the anchorage dependent and independent growth of ras transformed cells were severely curtailed by micromolar concentrations of BMS-186511. We also found that both H-ras and K-ras transformed cells are affected by this bisubstrate inhibitor. However, K-ras transformed cells appear to be less sensitive. The inhibition of FT activity in cells and the ensuing inhibition of ras transformed cell growth is further manifested in distinct morphological changes in cells. Cells flattened, became less refractile and grew in contact inhibited monolayer. Moreover, the highly diffused character of the actin cytoskeleton in the ras transformed cells was dramatically reverted to an organized network of stress cables crisscrossing the entire cells upon treatment with BMS-186511. All of these effects of BMS-186511 are limited to ras transformed cells that utilize farnesylated Ras, but are not seen in transformed cells that use geranylgeranyl Ras or myristoyl Ras. Significantly, these FT inhibitors did not produce any signs of gross cytotoxicity in untransformed, ras transformed cells or other oncogene transformed cells.

PMID: 7753553 [PubMed - indexed for MEDLINE]

J Med Chem. 1995 Jul 21;38(15):2906-21. Related Articles, Links

Farnesyl diphosphate-based inhibitors of Ras farnesyl protein transferase.

Patel DV, Schmidt RJ, Biller SA, Gordon EM, Robinson SS, Manne V.

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.

The rational design, synthesis, and biological activity of farnesyl diphosphate (FPP)-based inhibitors of the enzyme Ras farnesyl protein transferase (FPT) is described. Compound 3, wherein a beta-carboxylic phosphonic acid type pyrophosphate (PP) surrogate is connected to the hydrophobic farnesyl group by an amide linker, was found to be a potent (I50(FPT) = 75 nM) and selective inhibitor of FPT, as evidenced by its inferior activity against squalene synthetase (I50 (SS) = 516 microM) and mevalonate kinase (I50(MK) = > 200 microM). A systematic structure-activity relationship study involving modifications of the farnesyl group, the amide linker, and the PP surrogate of 3 was undertaken. Both the carboxylic and phosphonic acid groups of the beta-carboxylic phosphonic acid PP surrogate are essential for activity, since deletion of either group results in 50-2600-fold loss in activity (6-9, I50 = 4.6-220 microM). The farnesyl group also displays very stringent requirements and does not tolerate one carbon homologation (12, I50 = 17.7 microM), substitution by a dodecyl fragment (14, I50 = 9 microM), or introduction of an extra methyl group at the allylic position (18, I50 = 55 microM). Modifications around the amide linker group of 3 were more forgiving, as evidenced by the activity of N-methyl analog (21, I50 = 0.53 microM), the one carbon atom shorter farnesoic acid-derived retroamide analog (32, I50 = 250 nM), and the exact retroamide analog (49, I50 = 50 nM). FPP analogs such as 3, 32, and 49 are novel, potent, selective, small-sized, nonpeptidic inhibitors of FPT that may find utility as antitumor agents.

PMID: 7636851 [PubMed - indexed for MEDLINE]

DOCUMENT-IDENTIFIER: US 6808926 B1
TITLE: Repressing gene expression in plants

Abstract Text (1):
Posttranslational modification of histones, in particular acetylation and deacetylation are involved in the regulation of gene expression. Histone deacetylases remove acetyl groups from histone proteins. The present invention is directed to a method of regulating gene expression in a transgenic plant comprising, introducing into a plant a first chimeric nucleotide sequence comprising a first regulatory element in operative association with a coding sequence of interest, and an upstream activating sequence, and a second chimeric nucleotide sequence comprising a second regulatory element in operative association with a nucleotide sequence encoding histone deaceytlase and a nucleotide sequence encoding a DNA binding protein, and growing the transgenic plant. Furthermore, a method for regulating gene expression of an endogenous coding sequence of interest, or modifying a developmental, physiological or biochemical pathway in a plant is provided comprising introducing into a plant a chimeric nucleotide sequence comprising a regulatory element in operative association with a nucleotide sequence encoding histone deaceytlase fused with a nucleotide sequence encoding a DNA binding protein capable of interacting with an endogenous controlling sequence, for example an upstream activating sequence, and growing the transgenic plant. This invention also relates to novel histone deacetylase obtained from plants, to novel chimeric construct comprising these, or other histone deacetylase, and to transgenic plants, plant cells, or seeds comprising these chimeric constructs.